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Catalytic asymmetric synthesis of highly substituted pyrrolizidines†

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A catalytic asymmetric double (1,3)-dipolar cycloaddition reaction has been developed. Using a chiral silver catalyst, enantioenriched pyrrolizidines can be prepared in one flask from inexpensive, commercially available starting materials. The pyrrolizidine products contain a variety of substitution patterns and as many as six stereogenic centers.

Introduction

Pyrrolizidines constitute a large family of biologically active natural products and synthetic pharmaceutical agents.[1] They include plant-derived polyhydroxylated alkaloids such as alexine (**1**),[2] hyacinthacine B_2 (**2**),[3] and casuarine (**3**)[4] – compounds that have garnered significant interest as glycosidase and glycosyl transfer inhibitors[5] – as well as the lypophilic frog toxins exemplified by 223H (**4**).[6] In addition, several synthetic pyrrolizidines have been reported as drug candidates. For example, pyrrolizidines **5** and **6** are selective antagonists of 5-hydroxytryptamine receptor 4 (5-HT_4),[7,8] while **7** is a potent antagonist of human neurokinin receptor 1 (hNK_1).[9] Although several strategies have been developed to prepare pyrrolizidines,[10,11] they often require multi-step syntheses and do not readily provide access to a diverse array of substituent patterns. Moreover, the enantioselective synthesis of these frameworks can be challenging. Herein, we report the catalytic asymmetric preparation of pyrrolizidines from simple, inexpensive starting materials.[12] This methodology enables the programmable incorporation of a variety of functional groups, and provides direct access to an array of highly substituted pyrrolizidines (Fig. 1).

In the course of our synthetic studies toward the natural product acetylaranotin, we sought to prepare pyrrolidine **10** by a catalytic asymmetric (1,3)-dipolar cycloaddition (DCA) (Scheme 1).[13] Although there are several reports of catalytic asymmetric (1,3)-DCAs between α-imino esters and acrylates,[14–16] at the outset of our studies, there were no examples of enantioselective reactions between cinnamaldehyde-derived imines and simple, unsubstituted acrylates.[17] This might be related to the instability of compounds such as **8**, which are prone to polymerization upon standing. We were therefore pleased to find that adaptation of conditions originally developed by Oh and co-workers,[18] which utilize brucin-OL (**13**, Table 1) as a chiral ligand, provided the desired pyrrolidine **10** in excellent ee, albeit in modest yield.

A major side product formed in the reaction was isolated and characterized, and discovered to be pyrrolizidine **12**.[19,20] Pyrrolizidine **12** is presumably produced by condensation of pyrrolidine **10** with imine **8** or cinnamaldehyde (resulting from imine hydrolysis) to generate azomethine ylide **11**, which undergoes a second highly diastereoselective (1,3)-DCA with **9**. Pyrrolizidine **12** contains four stereogenic centers and is formed as a single diastereomer; the diastereoselectivity is consistent with an *endo*-selective (1,3)-DCA in which the dipolarophile approaches the face of azomethine ylide **11** opposite to the styrenyl and ester substituents. Given the importance of the pyrrolizidine framework in biologically active alkaloids and synthetic pharmaceutical agents, we sought to improve the yield and explore the substrate scope of this transformation.

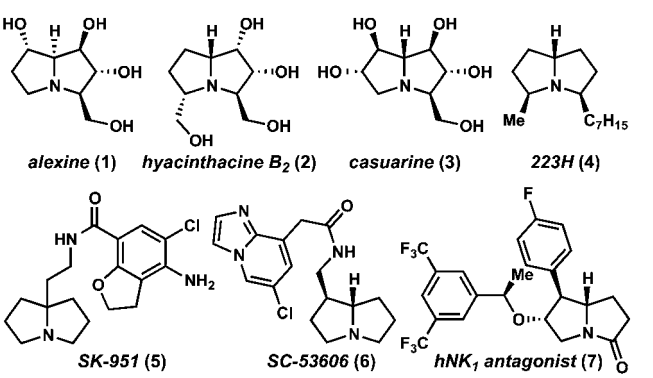

Fig. 1 Pyrrolizidine-containing natural products and pharmaceutical agents.

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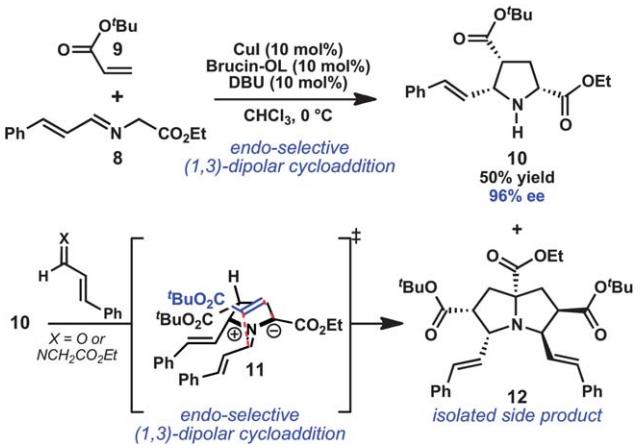
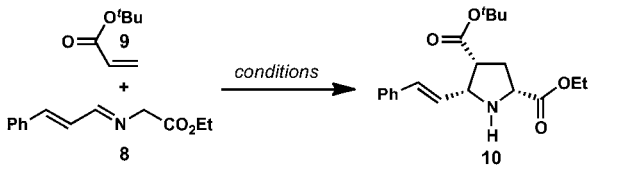
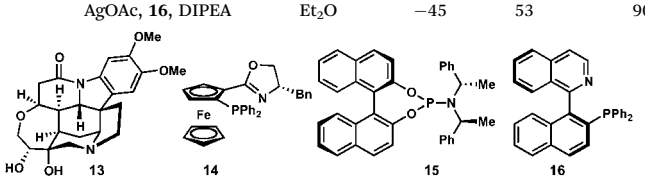


Scheme 1 Isolation of pyrrolizidine **12**.

Table 1 Optimization of the catalytic asymmetric (1,3)-DCA reaction between glycinate imine **8** and *tert*-butyl acrylate (**9**).



Entry	Catalyst/ligand/additive[a]	Solvent	Temp (°C)	Yield[b] (%)	ee[c] (%)
1	AgOAc, **14**	Et_2O	0	53	−63
2	$AgClO_4$, **15**, DABCO	PhMe	0	59	45
3	**AgOAc, 16, DIPEA**[d]	**THF**	**−45**	**62**	**90**
4	AgOAc, **16**, DIPEA	DCM	−45	36	78
5	AgOAc, **16**, DIPEA	$CHCl_3$	−45	5	—
6	AgOAc, **16**, DIPEA	PhMe	−45	60	90
7	AgOAc, **16**, DIPEA	Et_2O	−45	53	90



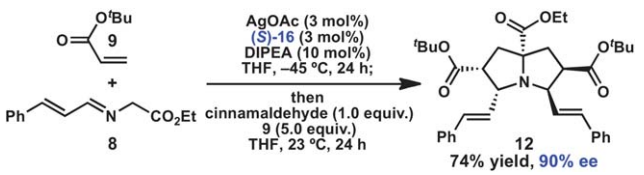
[a] See ESI† for reaction details. [b] Isolated yield. [c] Determined by SFC using chiral stationary phase. [d] 3 mol% each AgOAc and QUINAP, 10 mol% DIPEA.

Results and discussion

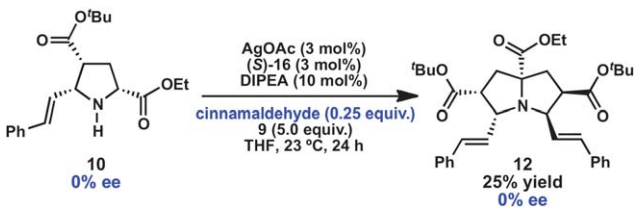
Although our initial discovery of pyrrolizidine formation was in the context of the CuI/brucin-OL catalyzed (1,3)-DCA, the need for a 24 h catalyst generation period, coupled with variability in the yield of pyrrolizidine formation, led us to pursue other catalyst systems for the purposes of this methodological study. Given that the enantiomeric excess of pyrrolizidine **12** is established during the first (1,3)-DCA, we initially conducted a survey of several chiral catalyst systems[16c,d,f] for their ability to provide enantioenriched pyrrolidine **10**; a selection of results are shown in Table 1. These studies revealed that good enantioinduction could be obtained using AgOAc (3 mol%) and (*S*)-QUINAP (**16**, 3 mol%) at −45 °C (Table 1, entry 3), conditions originally reported by Schreiber to catalyze (1,3)-DCA of aryl aldehyde-derived α-imino esters.[16c,21] Whereas halogenated solvents resulted in low yields and modest enantioselectivity, ethereal solvents were more promising, with THF providing the highest combination of yield and ee.

Having identified an operationally simple catalyst system to prepare pyrrolidine **10**, we began to investigate pyrrolizidine formation. We were pleased to find that treatment of a mixture of cinnamaldehyde-derived α-imino ester **8**, AgOAc (3 mol%), QUINAP (3 mol%) and DIPEA (10 mol%) with *tert*-butyl acrylate (**9**, 1.5 equiv.) in THF at −45 °C for 24 h, followed by addition of cinnamaldehyde (1.0 equiv.) and additional **9** (5.0 equiv.) with warming to 23 °C provided pyrrolizidine **12** in 74% yield and 90% ee (Scheme 2).[22,23] Notably, warmer temperatures are required for the second (1,3)-DCA, which proceeds very slowly at −45 °C. It is important that imine **8** is consumed before the reagents are added for the second cycloaddition; if **8** remains, it reacts rapidly and less selectively with *tert*-butyl acrylate upon warming to give **10**,[24] which can lead to the isolation of pyrrolizidine **12** in reduced ee.

It is frequently observed that reactions involving two, sequential catalytic asymmetric steps can benefit from a Horeau-type amplification of the ee.[25,26] In the present case, no change in ee is observed for pyrrolizidine **12** relative to pyrrolidine **10**. Indeed, exposure of racemic pyrrolidine **10** to 0.25 equivalents of cinnamaldehyde under otherwise standard conditions provided pyrrolizidine **12** in 25% yield and 0% ee, indicating that no kinetic resolution of pyrrolidine **10** occurs (Scheme 3). These data suggest that the diastereoselectivity of the second (1,3)-DCA is substrate-controlled. The enantioinduction for Ag-catalyzed asymmetric (1,3)-DCAs is hypothesized to result from two-point binding of the deprotonated α-imino ester to the chiral silver complex. However, azomethine ylide **11** (see Scheme 1) cannot achieve this two-point binding mode.



Scheme 2 Optimized conditions for preparation of pyrrolizidine **12**.



Scheme 3 Influence of chiral catalyst on second (1,3)-DCA.

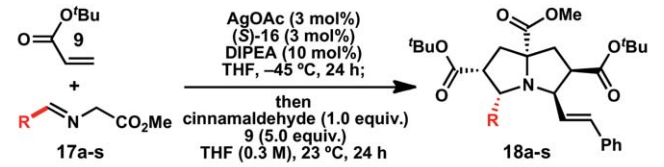
Although the silver complex accelerates the rate of the second (1,3)-DCA – perhaps by Lewis acid activation of the acrylate – it does not exert any significant "matching" or "mismatching" effect with the chiral azomethine ylide.

With conditions in hand to prepare pyrrolizidine **12** in good yield and high ee, attention turned to evaluating the substrate scope of the reaction (Table 2). A variety of substituted aryl aldehyde-derived α-imino esters **17** furnished the corresponding pyrrolizidines **18** in good yields with high enantioselectivity. Substitution at the *o*-, *m*-, and *p*-positions of the arene with both electron-donating and electron-withdrawing substituents is well-tolerated. In particular, α-imino esters bearing electron-withdrawing aryl substituents provide the pyrrolizidine products with uniformly high levels of enantioselectivity (Table 2, **18f–j**, **18m–o**). Notably, the α-imino ester derived from pyridine 3-carboxaldehyde is a suitable substrate, providing pyridyl-substituted pyrrolizidine **18r** in good yield and good ee (entry 18). Alternatively, the 2-pyridyl α-imino ester provided pyrrolizidine **18s** in low yield and modest ee (entry 19). It is possible that the proximal nitrogen results in an alternative binding mode between the azomethine ylide and the catalyst, decreasing the enantioselectivity during the first (1,3)-DCA.[27] In addition, the pyrrolidine intermediate or the pyrrolizidine product (**18s**) might bind to and inhibit the silver catalyst.

In some cases, the pyrrolizidine products were obtained in lower ee using our standard reaction conditions (*e.g.* compounds **18c–e**, **18q**).[28] It was determined that for these α-iminoesters, the first (1,3)-DCA proceeds slowly relative to the more electron-poor substrates; we reasoned that the remaining imine reacts with lower enantioselectively upon warming, which ultimately results in the formation of the pyrrolizidine with reduced ee. We hypothesized that increasing the catalyst loading should ensure complete consumption of the α-imino ester prior to warming the reaction for the second (1,3)-DCA. This hypothesis proved to be true; using 6 mol% each of AgOAc and (*S*)-**16**, pyrrolizidines **18c–e** and **18q** were obtained in good yields and high ee (Table 2, entries 3–5, and 17). Alternatively, the solubility of *p*-methoxy and 2-naphthyl α-iminoesters **17k** and **17p** was poor under our standard conditions; for these substrates the best results were obtained by lowering the overall reaction concentration (to 0.1 M *versus* 0.3 M) and increasing the catalyst loading to 6 mol% (Table 2, entries 11 and 16).

A variety of dipolarophiles can be used for the second (1,3)-DCA (Table 3). For example, use of *E*-1-nitro-2-phenylethylene as the second dipolarophile provides pyrrolizidine **19e** in 89% yield and 90% ee. This compound contains six stereogenic centers and is isolated as a *single* diastereomer. Use of methyl methacrylate provides pyrrolizidine **19d**, which contains an all-carbon quaternary center, in 91% yield and 90% ee.

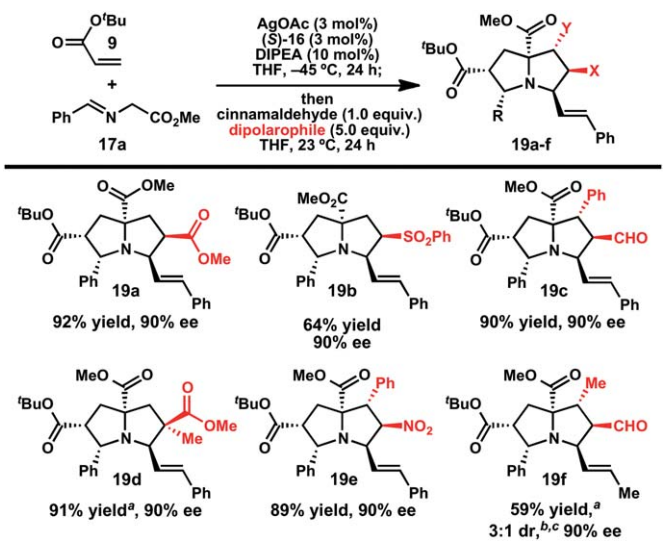
Table 2 Substrate scope: α-imino ester



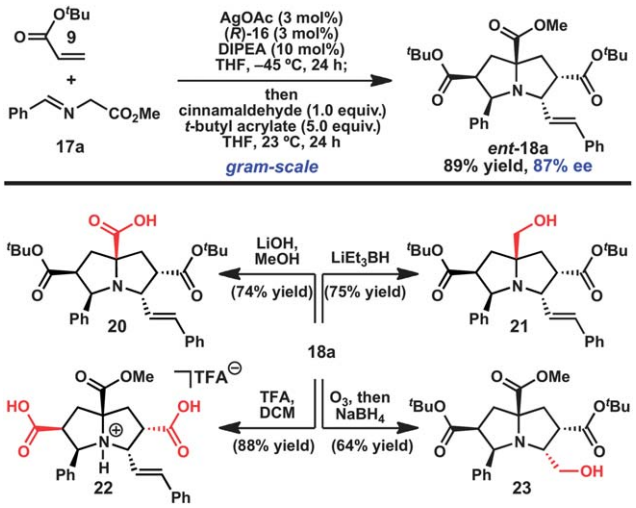
Entry		R	Yield[a] (%)	ee[b] (%)
1	18a	H	90	91
2	18b	2-Me	91	91
3[c]	18c	3-Me	83	88
4[c]	18d	4-Me	82	92
5[c]	18e	2,6-Me	78	88
6	18f	2-Me-5-F	87	93
7	18g	4-Cl	91	95
8	18h	4-Br	89	92
9	18i	4-NO$_2$	70	96
10	18j	4-CN	80	96
11[d]	18k	4-OMe	86	90
12	18l	2-MeO	72	90
13	18m	2-Cl	87	94
14	18n	2-Br	89	93
15	18o	3-Br	82	92
16[d]	18p	2-naphthyl	76	92
17[c]	18q	1-naphthyl	84	93
18	18r	3-pyridyl	90	90
19	18s	2-pyridyl	33	44

[a] Isolated yield. [b] Determined by SFC using chiral stationary phase. [c] 6 mol% each AgOAc and (*S*)-**16** were employed. [d] 6 mol% each AgOAc and (*S*)-**16** were employed at 0.1 M reaction concentration.

Table 3 Substrate scope: second dipolarophile



[a] 10.0 equivs. of dipolarophile were used. [b] For this reaction, crotonaldehyde was used instead of cinnamaldehyde. [c] Refers to *endo*/*exo* selectivity of the second (1,3)-DCA reaction.



Scheme 4 Gram-scale synthesis of ***ent*-18a** and selective derivatization.

Interestingly, α,β-unsaturated aldehydes appear to be uniquely well suited for generating the pyrrolidine-derived azomethine ylide for the second (1,3)-DCA. Attempts to employ aryl aldehydes (*e.g.* benzaldehyde) or alkyl aldehydes (*e.g.* 2-ethylbuytraldehyde) for the second (1,3)-DCA failed to provide the pyrrolizidine products in synthetically useful yields (see ESI†). We believe this unique reactivity of α,β-unsaturated aldehydes explains why standard catalytic, asymmetric (1,3)-DCAs are not plagued by unwanted pyrrolizidine formation, since α-imino esters derived from enals are rarely employed in methods development.

Using benzaldehyde-derived α-imino ester **17a**, the catalytic asymmetric double (1,3)-DCA reaction has been conducted on gram-scale, providing pyrrolizidine ***ent*-18a**[29] in 89% yield and slightly diminished ee (87%) (Scheme 4).[30,31] Importantly, this compound can be selectively modified to give several intermediates capable of further derivatization. For example, the more reactive and accessible methyl ester of ***ent*-18a** can be selectively saponified using LiOH or reduced using $LiEt_3BH$ to give carboxylic acid **20** or alcohol **21**, respectively. Alternatively, the *tert*-butyl esters can be cleaved upon treatment with trifluoroacetic acid (TFA) to give dicarboxylic acid **22**. Finally, the styrene of ***ent*-18a** can be oxidatively cleaved by ozonolysis and reduced *in situ* to provide amino alcohol **23** in 64% yield. These studies demonstrate that the individual functional groups of ***ent*-18a** can be chemoselectively modified.

Conclusions

In conclusion, a catalytic asymmetric double (1,3)-dipolar cycloaddition reaction has been developed. This reaction provides access to highly substituted, enantioenriched pyrrolizidines from inexpensive, commercially available starting materials. Depending on the second dipolarophile that is employed, pyrrolizidines containing as many as six stereogenic centers have been prepared with high levels of enantio- and diastereoselectivity. This methodology provides a versatile, programmable platform for the single-step synthesis of pyrrolizidines of unprecedented complexity. We expect that this reaction could be of use for the preparation of natural product analogues or new lead compounds for pharmaceutical studies.

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29 (*R*)-QUINAP was used.
30 On 0.15 mmol scale, **18a** could be prepared in 88% yield and 90% ee using 1 mol% catalyst in conjunction with a 48 h reaction period for the first (1,3)-DCA. Use of 1 mol% catalyst under standard conditions provided **18a** in 64% yield and 86% ee.
31 Reducing the amount of *tert*-butyl acrylate used in the second (1,3)-DCA to 1.5 equiv. provided **18a** in 74% yield and 91% ee.

